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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,793	03/22/2004	Teit E. Johansen	19313-001CON	2372

7590 09/27/2007

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EXAMINER	
BALLARD, KIMBERLY A	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
09/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,793	JOHANSEN ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *80-83 and 87-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *80-83 and 87-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/27/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Claims 80-83 have been amended and claims 87-90 have been added as requested in the amendment filed June 27, 2007. Claims 1-79 and 84-86 have been canceled. Following the amendments, claims 80-83 and 87-90 are pending in the current application.

Claims **80-83** and **87-90** are under examination in the instant office action.

Information Disclosure Statement

A signed and initialed copy of the March 23, 2004 IDS paper re-submitted June 27, 2007 is enclosed in this action.

Priority

In the response filed June 27, 2007, Applicants submit that the specification of the priority documents fully enable the claims, wherein each of the documents disclose methods of treating neurodegenerative disorders. Applicants therefore assert that one of skill in the art would have been able to rely on the teachings of the priority specifications to practice the claimed invention.

Applicant's arguments have been fully considered but they are not persuasive. As noted previously, the disclosure of the prior-filed provisional applications, Application Nos. 60/092,229 (filed 07/09/1998), 60/097,774 (filed 08/25/1998), and 60/103,908 (filed

10/13/1998), fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. While the provisional applications may generically disclose treatment of neurodegenerative disorders, they do not specifically disclose the instantly claimed method of treating or preventing a disorder of the eye comprising administering a cell line expressing a Neublastin polypeptide. Support for the instantly claimed method is first noted in the non-provisional Application No. 09/347,613, filed 07/02/199, now US Patent No. 6,593,133, particularly at column 20, lines 56-57 and column 21, lines 46-51. Accordingly, for purposes of prior art, the effective filing date of the instant claims is still **02 July 1999**.

Withdrawn Objections and Claim Rejections

Claim Objections

The objection to claims 81 and 82 for recitation of non-elected subject matter, as set forth in the previous Office action (03/26/2007) is withdrawn in view of Applicants' amendments to the claims.

Sequence Requirements

The objection to the specification and claims regarding sequence requirements, as set forth at p. 4 of the previous Office action (03/26/2007) is withdrawn in view of Applicants' amendments to the disclosure and claims.

Claim Rejections - 35 USC § 112

The rejection of claims 80-85 under 35 U.S.C. 112, first paragraph, as set forth at pp. 6-10 of the 03/26/2007 Office action is withdrawn in view of the amendments to the claims.

The rejection of claims 80-85 under 35 U.S.C. 112, second paragraph, as set forth at pp. 10-11 of the 03/26/2007 Office action is withdrawn in view of the amendments to the claims.

Claim Rejections - 35 USC § 102

The rejection of claims 80-85 under 35 U.S.C. 102(b) as being anticipated by Algvere et al. (*Graefe's Arch Clin Exp Ophthalmol.* March 1997; 235: 149-158) is withdrawn in view of the amendments to the claims.

The rejection of claims 80-85 under 35 U.S.C. 102(e) as being anticipated by US 2003/0059868 A1 by Greenwood et al., is withdrawn in view of Applicants' arguments. The priority documents of Greenwood et al. do not disclose a Neublastin polypeptide, and therefore cannot be relied upon as prior art under 35 U.S.C. 102(e).

The rejection of claims 80-85 under 35 U.S.C. 102(e) as being anticipated by US Patent 6,361,771 B1 to Tao et al., is withdrawn in view of Applicants' arguments. The

priority documents of Tao et al. do not disclose a Neublastin polypeptide, and therefore cannot be relied upon as prior art under 35 U.S.C. 102(e).

New Claim Rejections, Necessitated by Amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 80-83 and 87-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,641,749 to Yan et al. (issued June 24, 1997) in view of US 6,284,540 B1 to Milbrandt et al. (filed December 24, 1998; listed on Applicant's IDS).

The claims, as amended, are drawn to a method of treating a disorder of the eye comprising administering to the eye a genetically manipulated cell line that expresses a Neublastin polypeptide, wherein the polypeptide comprises an amino acid sequence that is at least 95% homologous to SEQ ID NO: 12, and wherein the disorder of the eye is macular degeneration, retinitis pigmentosa, or glaucoma. Additional claim limitations recite particular conserved cysteine residues within SEQ ID NO: 12 (claim 81), particular motifs of SEQ ID NO: 12 (claims 82 and 83), and wherein the Neublastin polypeptide comprises an amino acid sequence of SEQ ID NO: 9 (claim 87), 10 (claim 88), 11 (claim 89), or 12 (claim 90).

Yan et al. disclose methods of treating retinal ganglion cell degeneration caused by glaucoma by the intraocular implantation of glial cell line-derived neurotrophic factor (GDNF)-expressing cells (see paragraph spanning columns 4-5, and column 19, lines 28-30). Yan notes that GDNF has a larger spectrum of neurotrophic targets beyond mesencephalic dopaminergic neurons, and has been demonstrated to have neurotrophic efficacy both *in vivo* and *in vitro* in brain stem and spinal cord cholinergic motor neurons (see column 2, lines 10-23). In particular, Yan teaches that GDNF has been found useful for the treatment of nerve injury, such as for the treatment of retinal

ganglion cells damaged by optic neuropathies such as glaucoma (see background, columns 2-3). As such, variants and derivatives of GDNF are also taught as being useful for the disclosed therapeutic methods, such as protein products that are substantially homologous to GDNF (see column 6, lines 1-23). Yan discloses that the implanted cells may be transformed such that they produce GDNF, and that recombinant human cell lines or the patient's own cells (transformed *ex vivo* to produce the desired GDNF protein or GDNF protein variant prior to re-implantation) may be used for this purpose (see column 19, lines 28-63). Such cells would meet the recitation of a genetically manipulated cell line of instant claim 80. However, Yan does not teach the use of a neublastin polypeptide for such methods.

Milbrandt et al. disclose the neurotrophic factor artemin, which is another name for the instantly claimed neublastin protein (another name for the protein is enovin), and discloses an amino acid sequence that is 100% identical to the instantly claimed neublastin polypeptide of SEQ ID NO: 12. For example, a search of the relevant databases revealed the following:

```
RESULT 1
AAY84586
ID   AAY84586 standard; protein; 113 AA.
XX
AC   AAY84586;
XX
DT   25-JUL-2000  (first entry)
XX
DE   A first predicted human mature artemin polypeptide.
XX
KW   Human; artemin; growth factor; neurotrophic factor; trophic support;
KW   neuron; trigeminal ganglion neuron; nodose ganglion neuron;
KW   superior cervical ganglion neuron; midbrain neuron; Alzheimer's disease;
KW   peripheral neuropathy; amylotrophic lateral sclerosis; ischemic stroke;
KW   Parkinson's disease; Huntington's disease; acute brain injury;
KW   acute spinal cord injury; nervous system tumour; blastoma;
KW   multiple sclerosis; infection; enteric disease; idiopathic constipation;
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KW   Parkinson's disease; small cell lung carcinoma.
XX
OS   Homo sapiens.
XX
PN   WO200018799-A1.
XX
PD   06-APR-2000.
XX
PF   29-SEP-1999;   99WO-US022604.
XX
PR   29-SEP-1998;   98US-00163283.
PR   12-NOV-1998;   98US-0108148P.
PR   22-DEC-1998;   98US-00218698.
XX
PA   (UNIW ) UNIV WASHINGTON.
XX
PI   Milbrandt JD,  Baloh RH;
XX
DR   WPI; 2000-293109/25.
DR   N-PSDB; AAA12543.
XX
PT   Isolated artemin growth factor proteins and the nucleic acids that encode
PT   them, useful for treating a range of degenerative neuronal disorders such
PT   as Parkinson's disease and Huntington's disease.
XX
PS   Claim 4; Fig 3A; 96pp; English.
XX

SQ   Sequence 113 AA;

Query Match             100.0%;  Score 601;  DB 3;  Length 113;
  Best Local Similarity   100.0%;  Pred. No. 1.8e-55;
  Matches  113;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 AGGPGSRARAAGARGCRLRSQLVPVRALGLGHRSDELVRFRFCSGSCRRARSPHDLSLAS 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 AGGPGSRARAAGARGCRLRSQLVPVRALGLGHRSDELVRFRFCSGSCRRARSPHDLSLAS 60

Qy         61 LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG 113
              |||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG 113
```

Above, it is noted that the "Qy" (query) sequence is the instantly claimed SEQ ID NO: 12 and the "Db" (database) sequence is one that is disclosed by Milbrandt et al. Accordingly, the sequence disclosed by Milbrandt comprises the notes amino acid residues of claim 82, the motifs of claim 83, and the amino acid sequence of claim 90.

Further, Milbrandt discloses several other sequences that are identical to the instantly claimed SEQ ID NOs: 9, 10 and 11, thus addressing recited limitations of new claims 87-89. Milbrandt teaches that artemin is a neurotrophic factor that belongs to the GDNF/neurturin/persephin family of growth factors and promotes differentiation, maintains mature phenotype and provides trophic support, promoting growth and survival of neurons (see abstract). Artemin is thus taught as being useful for the providing trophic support to neurons, so as to inhibit atrophy, degeneration or death of neurons, such as in the treatment of disease conditions involving neuronal degeneration (see column 6, lines 15-29). Milbrandt notes that on the basis of structural similarity with GDNF, neurturin and persephin, artemin would be expected to promote the survival and growth of neuronal as well as non-neuronal cells, and to influence a broad spectrum of neuronal populations in the peripheral and central nervous systems (see column 20, lines 39-45). Milbrandt also teaches the use of cells transformed to express and secrete artemin for transplantation or engraftment into patients (see column 27, lines 8-29).

It would have been obvious to one of ordinary skill in the art to substitute the use of the growth factor artemin, as taught by Milbrandt, in the method of treating glaucoma comprising the transplantation of transformed cells expressing GDNF, as taught by Yan. Milbrandt discloses that artemin (i.e., neublastin) is a member of the GDNF/neurturin/persephin trophic factor family, and therefore would be expected to possess similar trophic activity for both neuronal and non-neuronal cells. Yan teaches that glaucoma causes the degeneration of retinal neurons, and Milbrandt teaches that

artemin is useful for treating conditions involving neuronal degeneration. Both Yan and Milbrandt teach the use of cells genetically manipulated to express the desired neurotrophic factor, and the subsequent transplantation of these cells into a patient. Hence, the skilled artisan would reasonably expect that artemin-expressing cells could be successfully used in a method for treating the degeneration of retinal neurons, such as in the treatment of glaucoma. Accordingly, the combined teachings of the above references render obvious the instant method of claims 80-83 and 87-90.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on Monday-Friday 9AM - 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kimberly Ballard, Ph.D.
September 21, 2007

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646